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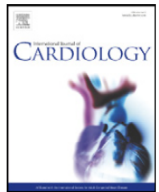
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# Serial cardiovascular magnetic resonance feature tracking indicates early worsening of cardiac function in Fontan patients

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## ABSTRACT

**Background:** In Fontan patients, attrition of ventricular function is well recognized, but early detection of ventricular dysfunction is difficult. The aim of this study is to longitudinally assess ventricular strain in Fontan patients using a new method for cardiac magnetic resonance (CMR) feature tracking, and to investigate the relationship between ventricular strain and cardiac systolic function.

**Methods and results:** In this prospective, standardized follow-up study in 51 Fontan patients, age  $\geq 10$  years, CMR and concomitant clinical assessment was done at the start of the study and after 2 years. CMR feature tracking was done combining the dominant and hypoplastic ventricles. Global longitudinal strain (GLS) ( $-17.3\%$  versus  $-15.9\%$ ,  $P = 0.041$ ) and global circumferential strain (GCS) ( $-17.7$  versus  $-16.1$ ,  $P = 0.047$ ) decreased over 2 years' time. Ejection fraction (EF) (57%), cardiac index (CI) ( $2.7$  l/min/m<sup>2</sup>) and NYHA functional class (97% in class I/II) were preserved. The strain values of the combined dominant and hypoplastic ventricles were significantly worse compared to those of the dominant ventricle only (GLS  $-16.8$  ( $-19.5$  to  $-14.0$ ) versus  $-18.8$  ( $-21.3$  to  $-15.3$ ) respectively,  $P = 0.001$ , GCS  $-18.3$  ( $-22.1$  to  $-14.8$ ) versus  $-22.5$  ( $-26.3$  to  $-19.4$ ) respectively,  $P < 0.001$ ).

**Conclusions:** This study showed a decrease in cardiac strain over 2 years in Fontan patients without clinical signs of Fontan failure, where EF, CI and clinical status were still preserved. Cardiac strain might be a sensitive early indicator of systolic ventricular decline. Furthermore, combined strain of the hypoplastic and dominant ventricles seems a more accurate representation of cardiac strain in functionally univentricular hearts.

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## 1. Introduction

Ventricular dysfunction has been reported to be a risk factor for morbidity and mortality in patients with a Fontan circulation, deeming early detection important [1]. Reliable quantification of ventricular function in patients with a univentricular heart is challenging due to the complex and diverse cardiac morphology. Ejection fraction (EF), a potent and reliable indicator of ventricular systolic function in structurally normal hearts, is less suitable in functionally univentricular hearts [2]. Cardiovascular imaging has evolved from obtaining qualitative diagnostic information towards more quantitative assessment methods. In recent years, strain, or myocardial deformation, has been used for assessment of ventricular function in various cardiovascular diseases. One of its

advantages is that, as opposed to EF, ventricular deformation is measured directly, without geometric assumptions [3].

Strain imaging can be conducted with speckle tracking echocardiography, which is deemed useful in assessing ventricular function and predicting outcome in Fontan patients [4–6]. Recently introduced, cardiac magnetic resonance (CMR) feature tracking offers potential qualitative advantages [7]. So far, cross-sectional studies have proven the feasibility of CMR feature tracking in the Fontan population [8,9], and have shown differences between left and right ventricular morphology [10], but serial data is lacking.

To date, CMR strain in functionally univentricular hearts has been measured in the dominant ventricle. However, almost all functionally univentricular hearts have a hypoplastic second ventricle. Although the exclusion of the hypoplastic ventricle might be justifiable from a morphologic perspective, it neglects to acknowledge that the hypoplastic ventricle functions as an integral 'ventricular unit' with the dominant ventricle, potentially hampering its net energetic effectiveness [11]. Contractile energy can be lost due to dyskinetic regions such as in the hypoplastic ventricle. By only measuring strain in the dominant ventricle,

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<sup>1</sup> All above mentioned authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

including a virtual (incomplete or hardly-existing) interventricular septum, this potential loss of energy would be ignored. We hypothesize that including the hypoplastic ventricle in the strain measurements will reduce global ventricular strain values, which would be a more representative reflection of the energetic effectiveness of the ventricular unit.

The aim of this study was to serially assess ventricular strain in a cohort of children and adults with a Fontan circulation using CMR feature tracking and to investigate the relationship between ventricular strain and cardiac systolic function over time. In addition, a novel, more appropriate and comprehensive method for CMR feature tracking in Fontan physiology is introduced.

## 2. Methods

### 2.1. Study population and design

Fontan patients aged 10 years and older, followed at the Center for Congenital Heart Disease, University Medical Center Groningen, The Netherlands undergo a standardized, biennial diagnostic work up, including ECG, Echocardiography, CPET and CMR. All patients who underwent CMR in 2012 and 2014 were included. Only patients with a ventricular septal defect (VSD) were included, which means that patients with pulmonary atresia and an intact ventricular septum were excluded since in that case the dominant and hypoplastic ventricle do not function as a communicating unit. The investigation conforms to the principles outlined in the Declaration of Helsinki. The institutional ethics committee approved the conduct of this investigation. Informed consent was obtained from all study participants and/or their parents.

### 2.2. Clinical variables

Patient characteristics were collected from medical records. Fontan-associated complications were defined as protein-losing enteropathy (PLE), liver cirrhosis and/or arrhythmia. Cardiopulmonary exercise testing (CPET) was performed on an upright cycle ergometer in children and on a treadmill in adults as previously described [12]. Peak  $\text{VO}_2$  ( $\text{pVO}_2$ ) was calculated as the mean of the last 30 s during exercise and was indexed for body weight ( $\text{pVO}_2$  indexed). The  $\text{pVO}_2$  as percentage of predicted was calculated using reference values [13,14]. Only CPETs that were done within one month of the CMR study were included. Adequate performance of CPET was defined as  $\text{RER} > 1.0$  in agreement with guidelines for both the pediatric population as well as for adults with heart failure [13,15]. Patients with an  $\text{RER} < 1.0$  were excluded.

### 2.3. CMR acquisition and analysis

CMR studies were performed on a 1.5 Tesla system (Siemens, Magnetom Avanto, Erlangen, Germany). Sedation was not applied. The CMR protocol included a stack of short-axis slices from the base to the apex of the heart using cine-steady-state free precession with end-expiratory breath holding. The following scan parameters were used: slice thickness 6 mm; slice gap 4 mm; TR 2.7–3.4 ms; TE 1.1–1.7 ms; flip angle 80–90°; matrix 171–192; voxel size  $1.25 \times 1.25 \times 8.0$  mm and  $1.7 \times 1.7 \times 6.0$  mm. Imaging analysis was performed using Qmass (v 7.6.14.0 Medis Medical Imaging Leiden, the Netherlands). In all views, 25 images per cardiac cycle were acquired which yielded a temporal resolution of 20–40 ms, depending on heart rate. End-systolic and end-diastolic phase were visually selected, using the largest and smallest systemic ventricular cavity on the longitudinal and short axis views. The contours of the systemic and hypoplastic ventricle were manually drawn on epicardial and endocardial borders from the most apical to the most basal short axis slice. The end-systolic and end-diastolic blood volumes were calculated from the endocardial contours; both the volumes of the dominant and hypoplastic ventricle were included for the calculation of EF. Cardiac output was detracted from aorta flow: Two-dimensional velocity encoded CMR flow measurements

were performed using 2-D gradient echo Fast Low Angle SHot (FLASH), acquired during normal respiration with retrospective cardiac gating. Aorta flow was analyzed using QFlow (v 5.6, Medis Medical Imaging, Leiden, The Netherlands). Aorta contours were semi-automatically generated, and thereafter manually adjusted. Automated background offset correction was performed. Cardiac index (CI) was calculated using body surface area (BSA).

### 2.4. CMR feature tracking

CMR feature tracking analysis was performed using the validated software Qstrain (v 7.6.14.0 Medis Medical Imaging Leiden, the Netherlands) [16–18]. Analysis was performed by manually tracing the endocardium and triggering the automatic computation. The tracking contour during movement of the myocardium was visually assessed, and the analysis was repeated if inadequate. Notably, CMR feature tracking was performed using two methods in all patients. First, the conventional method of only measuring the strain of the dominant ventricle was done. Second, a combined measurement of the dominant and the hypoplastic ventricle was done (Figs. 1 and 2). In the hearts with an indistinguishable hypoplastic ventricle, only the dominant ventricle was measured. The values of global peak strain (%) and strain rate (1/s) were recorded from the three strain parameters. Furthermore, longitudinal strain of the free wall, i.e. the non-septal wall of the dominant ventricle was recorded. Global longitudinal strain (GLS, expressed as negative value) was assessed in a four-chamber view. It represents base-apex shortening. Global circumferential strain (GCS) and global radial strain (GRS) was assessed in the short-axis view at midpapillary level. GCS represents shortening along the circular perimeter (expressed as negative value). GRS depicts thickening towards the center of the ventricular cavity (expressed as positive value).

### 2.5. Statistical analysis

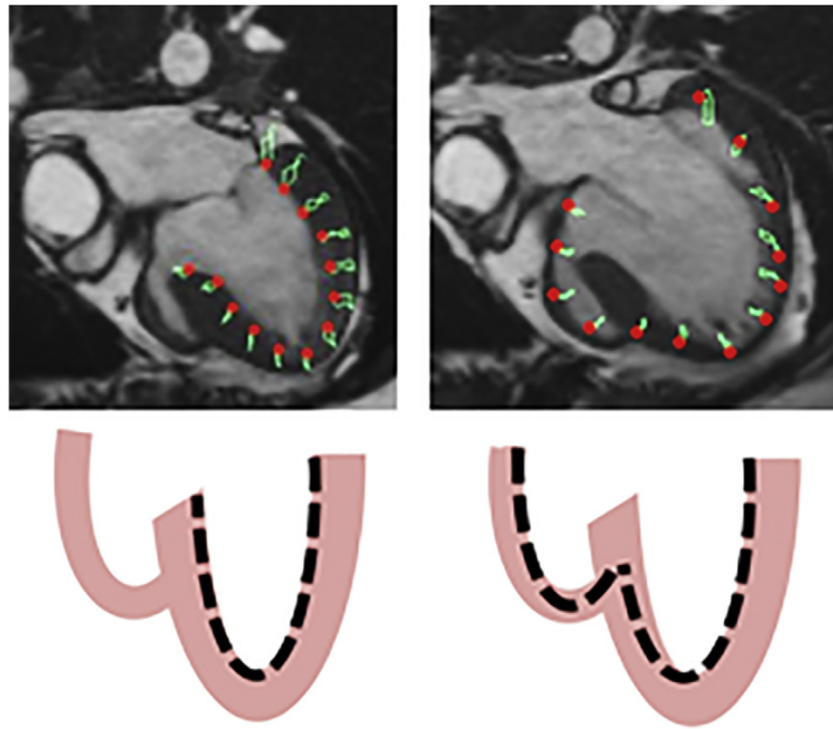
All continuous variables were tested for normality using the Shapiro-Wilk test and are presented as mean ( $\pm$ SD) if parametric or as median (25th – 75th IQR) if nonparametric. Categorical data were presented as frequency (percentage of total). Comparisons between strain measurements of the dominant ventricle only versus the combined dominant and hypoplastic ventricles were made with the paired Student *t*-test or Wilcoxon signed rank test. For the longitudinal analysis, the differences between baseline and follow-up strain parameters were calculated. Additional analysis with strain parameters indexed for BSA was done to correct for age and developmental influences. Strain parameters were stratified by sex to assess whether there are any sex differences. Pearson's correlation coefficient or Spearman's rank order coefficient were used to analyze linear relationships between strain parameters and traditional cardiac function parameters (EF, CI). Both baseline and follow-up parameters of all patients who had two measurements were included in the correlation analysis. All analyses were performed using IBM SPSS Statistics for Windows, V23.0. A *P*-value  $\leq 0.05$  was considered statistically significant. The intra-observer and inter-observer variability for strain measurements were assessed using the coefficient of variation (defined by the SD of the differences divided by the mean) (Supplementary Table 1).

## 3. Results

### 3.1. Patient characteristics and clinical findings

Fifty-one patients with a median age of 15.7 (12.9–22.0) years were included at baseline, 46 patients at the second visit. The median time passed between the first and the second outpatient visit was 2.1 years (2.0–2.3). See Table 1 for patient characteristics.





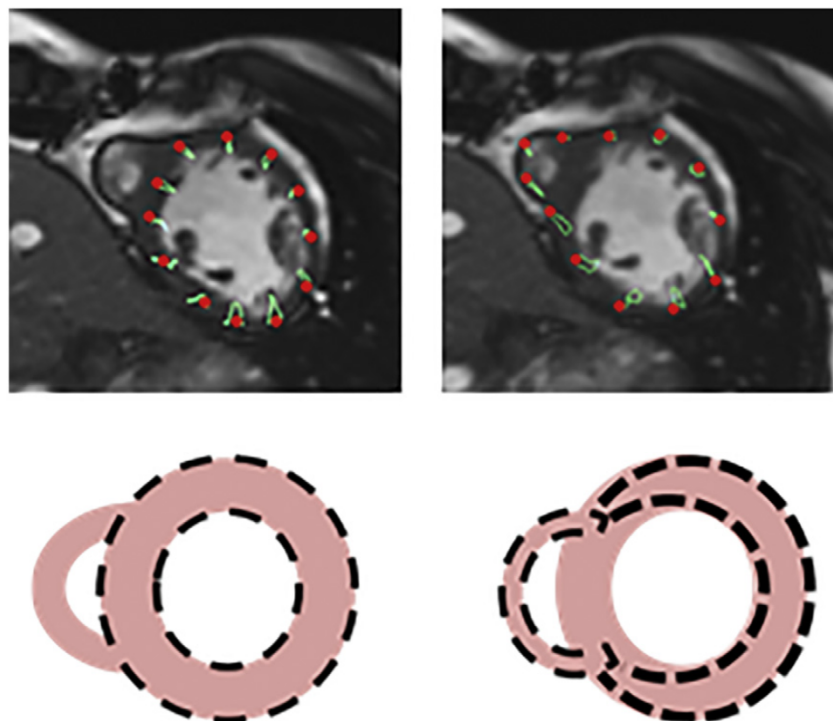
**Fig. 1.** Longitudinal strain measurements. Longitudinal CMR feature tracking methods, depicted in four-chamber view. The standard method, depicted on the left, only includes the dominant ventricle. The novel measurement method introduced in this study, depicted on the right, includes both the dominant and hypoplastic ventricles.

### 3.2. Reproducibility of CMR strain measurements

The inter- and intra-observer variability (intraclass correlations) comparison for all strain and strain rate measurements showed good agreement (Supplementary Table 1).

### 3.3. CMR strain measurements - dominant ventricle versus dominant and hypoplastic ventricles combined

Baseline GLS and GLS rate (GLSR) and GCS and GCS rate (GCSR) were significantly lower for the combined ventricle method when compared



**Fig. 2.** Circumferential and radial strain measurements. Circumferential and radial CMR feature tracking, depicted in short axis midpapillary view. The standard method, depicted on the left, only includes the dominant ventricle. The novel measurement method introduced in this study, depicted on the right, includes both the dominant and hypoplastic ventricles.

**Table 1**  
Baseline characteristics.

	N = 51
Female	24 (47%)
Age at outpatient clinic visit, years	15.7 (12.9–22.0)
Time since Fontan completion, years	11.6 (6.6–18.1)
Diagnosis	
Tricuspid atresia	23 (45%)
Double inlet left ventricle	11 (21%)
Hypoplastic left heart syndrome	3 (6%)
Atrioventricular septal defect	8 (16%)
Mitral atresia	3 (6%)
Other	3 (6%)
Dominant ventricular morphology	
Left	40 (78%)
Right	11 (22%)
Type Fontan	
Lateral tunnel	28 (55%)
Extracardiac conduit	18 (35%)
Atriopulmonary connection	3 (6%)
Kawashima <sup>a</sup>	2 (6%)
NYHA functional class	
I	25 (49%)
II	24 (47%)
III	2 (4%)
SpO <sub>2</sub> saturation at rest %	91 ± 4.5
Ejection fraction %	56 ± 7.7
Cardiac index l/min/m <sup>2</sup>	2.7 (2.1–3.2)
NTproBNP ng/l	103 (52–150)
Cardiopulmonary exercise test (n = 33)	
pVO <sub>2</sub> indexed, ml/min/kg	26.1 (21.7–33.1)
pVO <sub>2</sub> predicted, %	61.0 (45.5–74.5)
Fontan-associated complications	
Protein losing enteropathy	2 (4%)
Liver cirrhosis	1 (2%)
Arrhythmia	6 (12%)

Data are presented as mean (±SD), median (25th–75th IQR) or frequency (%).

NYHA = New York Heart Association, NTproBNP = N-terminal pro brain natriuretic peptide, pVO<sub>2</sub> = peak oxygen uptake.

<sup>a</sup> One of the 2 Kawashima patients went on to have an extracardiac tunnel from the liver veins to vena cava superior, the other had an extracardiac tunnel from the liver veins to the right pulmonary artery.

to the conventional ‘dominant ventricle only’ method (Table 2). In contrast, the values for GRS and free wall longitudinal strain (LS) did not differ significantly between the 2 methods.

#### 3.4. Cardiac strain and traditional cardiac function parameters

A significant negative correlation was found between EF and GLS, GLSR and GCS only of the combined ventricles (Spearman's rho ( $r_s$ ) = −0.362,  $P$  = 0.001;  $r_s$  = −0.237,  $P$  = 0.030;  $r_s$  = −0.357,  $P$  = 0.001 respectively). Cardiac index correlated with GLSR, GCS, GCSR, GRS and GRSR of the combined ventricles ( $r_s$  = −0.307,  $P$  = 0.006;

$r_s$  = −0.228,  $P$  = 0.046;  $r_s$  = −0.343,  $P$  = 0.002;  $r_s$  = 0.248,  $P$  = 0.029;  $r_s$  = 0.429,  $P$  < 0.001) and GCSR and GRSR of the dominant ventricle ( $r_s$  = −0.324,  $P$  = 0.005;  $r_s$  = 0.278,  $P$  = 0.010) (Supplementary Table 2). Combined GCSR and combined GRS correlated significantly with pVO<sub>2</sub> indexed ( $r_s$  = −0.23,  $P$  = 0.043 and  $r_s$  = 0.24,  $P$  = 0.044 respectively). None of the dominant ventricle only strain parameters correlated with CPET parameters. Strain values did not differ significantly between patients in NYHA class I and II. However, the 2 patients in NYHA class III had remarkably worse strain values than those in NYHA class I and II (GLS −14% versus −16%, GCS −11% versus −17%, GRS 29% versus 35% respectively). In the 7 patients with a Fontan-related complication, strain values were lower compared to the patients without complications (GLS −15% versus −18%, GCS −16 versus −19%, GRS 24% versus 40% respectively). No significant sex differences were found with regards to strain parameters.

#### 3.5. Cardiac function over time

The analysis of 46 patients who underwent 2 consecutive CMR measurements showed significant reduction in combined GLS (−17.3 (−19.5 to −14.3) to −15.9 (−17.7 to −13.9),  $P$  = 0.041) and combined GCS (−17.7 (−21.7 to −15.1) to −16.1 (−19.2 to −13.3),  $P$  = 0.047) as well as systemic ventricle GCS (−21.6 (−27.0 to −19.4) to −19.0 (−21.1 to −16.0)  $P$  = 0.037) over time, also when values were indexed for BSA (Supplementary Table 3). EF and CI as well as indexed end-systolic and end-diastolic ventricular volumes did not change over the two years period. Indexed ventricular mass increased significantly (82.8 (70.1–96.1) to 98.1 (81.1–118.1)  $P$  < 0.001. Clinically, no deterioration of NYHA functional class or CPET values was noted in this period. No new Fontan-associated complications occurred during this follow up period. In comparison to those whose strain parameters (GLS or GCS) remained stable, those whose GLS deteriorated had a (non-significant) trend towards lower exercise capacity (pVO<sub>2</sub> 30 versus 24 ml/min/kg), larger indexed end-diastolic volumes (76 versus 78 ml/m<sup>2</sup>), lower EF (59 versus 54%) and CI (2.9 versus 2.5 l/min/m<sup>2</sup>), and higher NYHA functional class at baseline. Patients with worsening GLS over time had higher levels of baseline NTproBNP than those whose GLS remained stable (63.5 versus 114 ng/l,  $P$  = 0.034).

#### 4. Discussion

The major findings of this prospective follow-up study are that cardiac strain in clinically stable Fontan patients deteriorated significantly in a two year period, whereas EF, CI and functional status remained preserved. To our knowledge, this is the first study that serially investigated CMR strain in Fontan patients at a standardized follow up period. Furthermore, measuring the strain of the combined ventricular unit, that consists of both the dominant and the hypoplastic ventricle, reveals

**Table 2**  
Comparison between baseline strain measurement methods (n = 51).

	Dominant ventricle	Combined ventricles (n = 45)*	Significance (P-value)
GLS %	−18.8 (−21.3– −15.3)	−16.8 (−19.5 to −14.0)	<b>0.001</b>
GLSR 1/s	−0.9 (−0.9 to −0.8)	−0.8 (−1 to −0.65)	<b>0.004</b>
Free wall LS %	−20.5 (−23.9 to −16.6)	−20.1 (−25.1 to −15.5)	0.560
Free wall LSR 1/s	−0.9 (−0.9– −0.8)	−0.9 (−0.9 to −0.8)	0.975
GCS %	−22.5 (−26.3 to −19.4)	−18.3 (−22.1 to −14.8)	<b>&lt;0.001</b>
GCSR 1/s	−0.9 (−1.1 to −0.8)	−0.8 (−0.9 to −0.6)	<b>&lt;0.001</b>
GRS %	35.7 (24.7–50.4)	39.0 (23.3–54.6)	0.798
GRSR 1/s	1.2 (0.9–1.5)	1.2 (0.8–1.5)	0.986
EDV ml/m <sup>2</sup>	57.2 (45.3–67.3)	63.2 (52.1–73.8)	<b>&lt;0.001</b>
ESV ml/m <sup>2</sup>	22.9 (17.9–29.8)	26.5 (19.8–36.6)	<b>&lt;0.001</b>
Mass g/m <sup>2</sup>	68.6 (54.1–82.9)	81.1 (69.5–94.5)	<b>&lt;0.001</b>

Baseline strain measurements, values are presented as median (25th–75th IQR).

EDV = end-diastolic volume, ESV = end-systolic volume, GCS = global circumferential strain, GCSR = global circumferential strain rate, GLS = global longitudinal strain, GLSR = global longitudinal strain rate, GRS = Global radial strain, GRSR = global radial strain rate.

\* The hypoplastic ventricle was not visible in 6 patients.



significantly worse strain values than measurements of the dominant ventricle alone. This indicates that the net effective performance of functionally univentricular hearts may be worse than previously presumed.

With the advent of high-resolution, 3-dimensional imaging techniques, our understanding of cardiac architecture and its relation to function has evolved immensely. Biventricular, morphologically normal hearts consist of a heterogeneous 3-dimensional meshwork of myocytes whose orientation partially determine ventricular function [19,20]. The function of the ventricles is linked. This ventricular interdependence [21] means that the left ventricle is important for right ventricular function and vice versa [22–24]. The ventricular septum plays a crucial role: it ensures interaction between the right and left ventricle [25] and contributes to the forceful ejection of blood from both ventricles during systole [26].

The architecture of functionally univentricular hearts differs from that of morphologically normal hearts [27]. Their myocardium seems to be inherently more fibrotic than that of normal hearts [28]. Ventricular adaptation and structural remodeling of the ventricle occurs due to extreme loading conditions: volume overload before and after birth leads to ventricular overgrowth and dilation followed by volume deprivation after Fontan completion, with consequently disturbed systolic and diastolic properties [29,30]. Furthermore, ventricular interdependence is impaired in functionally univentricular hearts. The role of ventricular function in Fontan failure is insufficiently understood. Fontan failure presents with a heterogeneous involvement of extracardiac organ systems such as the liver [31], the lungs [32], the veins as well as the lymphatics [33], not necessarily associated with apparent signs of ventricular dysfunction [34]. On the other hand, ventricular dysfunction, both systolic and diastolic, has been shown to be involved in the pathophysiology of Fontan failure and is predictive for a higher risk of late death [35].

This study in a young Fontan cohort with a median time after Fontan completion of 11 years suggests that discrete ventricular dysfunction, assessed by strain, exists early on, before decline of conventional cardiac function variables and clinical signs of Fontan failure. One explanation for early ventricular dysfunction could be early cardiac fibrosis. A CMR T1 relaxometry study of pediatric Fontan patients indicated that myocardial fibrosis is present early on and has a negative influence on cardiac contractility [36]. Ghelani et al. found that although Fontan patients with a right ventricular morphology had lower GCS compared with those with left ventricular morphology, their EF was similar [10], indicating that strain is a more sensitive marker for myocardial dysfunction. The fact that in the current study with relatively young Fontan patients, almost all patients had a preserved EF while strain values deteriorated, supports this theory.

To our knowledge, previous CMR feature tracking studies in Fontan hearts only analyzed the strain of the dominant ventricle, ignoring the hypoplastic ventricle that is connected to the dominant ventricle by means of a VSD [11]. Morphologically, the two ventricles are separate entities and artificially separating the two ventricles when measuring strain may seem justifiable. However, this raises two concerns: firstly, methodically speaking, due to the partially missing ventricular septum, delineating only the dominant ventricle inevitably requires anatomical assumptions of a virtual septum and poses associated technical difficulties [37]. Moreover, the area of the VSD is ignored out of necessity. Therefore, inclusion of the septum in CMR strain measurements, as it has been reported up to now, will likely lead to arbitrary and inaccurate representation of ventricular systolic function. Strain analyses in patients with a functionally univentricular heart with inclusion of the hypoplastic ventricle has been described previously using echocardiography speckle tracking analysis [38], however, no direct comparison with the conventional “dominant ventricle only method” was provided.

The second, and more important concern is the fact that both ventricles, dominant and hypoplastic, form a single functional ventricular unit with a unified contractile performance. In functionally univentricular hearts, ventricular interdependence is unfavorable. The septum is

often fibrotic and less contractile and abnormalities of septal movement impact global systemic ventricular function [39]. The hypoplastic ventricle in hypoplastic left heart syndrome has been shown to negatively affect diastolic performance of the systemic ventricle [40–42], while hypoplastic ventricle morphology and especially hypertrophy of the interventricular septum are associated with worse outcome [43,44]. The hypoplastic ventricle is often dyskinetic and by only measuring strain in the dominant ventricle, the negative effect of the hypoplastic ventricle on ventricular performance is ignored. Comparisons of strain values derived from the dominant ventricle to those derived from the combined dominant and hypoplastic ventricular unit, revealed significantly worse strain patterns in the latter. Therefore, we conclude that strain values of the dominant ventricle alone overestimate the net ventricular performance in Fontan patients. Measuring the strain of the combined ventricular unit provides a more accurate representation of its net energetic effectiveness.

Furthermore, in a population of relatively young and clinically stable Fontan patients, the serial nature of the measurements showed a significant attrition of longitudinal and circumferential strain over a period as short as 2 years, as opposed to the traditional clinical parameters such as EF, which did not decline. Radial strain and the various strain rates also seem to be insensitive to subtle changes, which has been recognized previously [45]. Previous studies on echocardiography-derived strains indicated a parabolic age-dependency with a maximum of strain values around puberty [46]. Reference values for CMR-derived strains in children and adolescents are sparse, however André et al. confirmed the parabolic relationship of age and CMR strain, and suggested the use of BSA as most accurate in correcting for the physiological changes over time [47]. Indexing the strain parameters for BSA in the current study, did not affect the deterioration that occurred in longitudinal and circumferential strain over the two year period, confirming that the observed reduction in strains rather represent a deterioration in function than physiological changes. Interestingly, the combined strain measurement showed a stronger deterioration over time than the dominant ventricle strain measurement.

The 2-year interval period used in this study is relatively short, which might explain why there are little changes in cardiac and functional status, however, the fact that strain values do decrease in such a short period highlights the importance of frequent check-ups. Since regular CMR control is part of the routine care for Fontan patients, it seems feasible to include CMR feature tracking analysis in order to detect ventricular systolic dysfunction at an early time.

This study has some limitations, including a relatively small sample size, although to the best of our knowledge no larger series of Fontan patients with serial CMR feature tracking analysis has been reported to date. The small sample size did not allow for comparison between subgroups, such as dominant right ventricular morphology versus left ventricular morphology and it made it impossible to associate strain parameters with outcome. This needs to be addressed in adequately powered follow-up studies. Furthermore, in the current study, no late gadolinium enhancement analysis was done. This would be a useful addition in order to evaluate myocardial fibrosis in future studies. Patients with ventricular dysfunction requiring pacemakers and defibrillators were excluded from CMR analysis, inducing a potential selection bias. However, this restriction of CMR compatibility will be encountered also in clinical practice. The prospective, standardized nature of the current study, however, minimizes referral bias and favors the studied cohort being representative for Fontan patients in the current era.

## 5. Conclusion

In conclusion, this prospective follow-up study of a relatively young and clinically stable cohort of Fontan patients shows a significant decrease in cardiac strain over a two year period, while EF, CI and clinical status remained preserved. This suggests that cardiac strain might be a sensitive early indicator of ventricular decline. Follow-up studies are



needed to explore if decline in strain is predictive for clinical deterioration and outcome. Furthermore, this study provides an alternate approach to CMR feature tracking in Fontan patients and indicates that measuring the combined strain of both the hypoplastic and dominant ventricles may well be a more accurate representation of the net ventricular performance in functionally univentricular hearts.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.12.041>.

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None.

## Conflict of interest

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